NDA 204,684

Miltefosine (Impavido®) for the Treatment of Visceral, Mucosal and Cutaneous Leishmaniasis

FDA Briefing Document for the Anti-Infective Drugs Advisory Committee Meeting

October 18, 2013

Sponsor: Paladin Therapeutics

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2 Background

Paladin Therapeutics submitted NDA 204, 684 for miltefosine (Impavido®) 50 mg capsules for oral administration on April 19, 2013, seeking approval for the treatment of visceral leishmaniasis caused by *L. donovani* and for the treatment of mucosal and cutaneous leishmaniasis caused by members of the subgenus *Viannia*. The FDA granted miltefosine orphan designation in October 2006 and Fast Track Designation in May 2010. The NDA was granted a priority review with a goal date of December 19, 2013.

Miltefosine is an alkyllysophospholipid analogue drug with *in vitro* activity against the promastigote and amastigote stages of *Leishmania* species. Miltefosine is registered in Germany as a topical drug to treat cutaneous cancers. As an oral agent, it is registered in Germany, several countries in South America and the Indian subcontinent for the treatment of visceral and cutaneous leishmaniasis. Miltefosine was included in the WHO essential medicines list as an anti-leishmaniasis medicine in March 2011[1].

2.1 Leishmaniasis

Leishmania organisms are intracellular protozoan parasites that are transmitted to a mammalian host by the bite of the female phlebotomine sandfly. The genus is divided into two subgenera, *Leishmania* and *Viannia*. *Leishmania* subgenus includes *L. donovani, L. chagasi/infantum, L. tropica, L. major, L. aethiopica, L. mexicana and L. amazonensis*. The subgenus *Viannia* includes *L. braziliensis, L. peruviana, L. guyanensis and L. panamensis*. Traditionally, *Leishmania* infections that occur in Asia, Africa, Europe and the Middle East are designated Old World, while infections that occur in the Americas are designated New World.

The main clinical syndromes are visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML).

Visceral leishmaniasis is the result of systemic infection. The WHO estimates that approximately 400,000 new cases of VL occur annually world-wide, and 90% of all cases of VL occur in six countries: India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil. VL is progressive over months or years. Clinical manifestations include fever, hepatomegaly, splenomegaly, and bone marrow involvement with pancytopenia. VL is fatal if untreated. The usual causative agents are *L. donovani* in the Indian Subcontinent and Africa, *L. chagasi/infantum* in South and Central America and in the Middle East. IV liposomal amphotericin B (AmBisome®) was FDA approved in 1997 for the treatment of VL. Other therapies used include amphotericin B deoxycholate, pentavalent antimony preparations and parenteral paromomycin. Antimonials are not recommended for use in the Indian subcontinent because of resistance. HIV co-infection adversely affects the course of VL, resulting in higher mortality and multiple relapses after treatment.

[1] http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf

Cutaneous leishmaniasis usually presents as one or more skin ulcers at the site of the sandfly bite. Approximately 0.7-1.2 million new CL cases occur annually world-wide[2]. Approximately 75% of the world's CL cases occur in ten countries: Iran, Syria, Algeria, Ethiopia, North Sudan, Afghanistan, Costa Rica, Brazil, Colombia and Peru. In the United States, CL may be seen in returning travelers following exposure in endemic regions, and in American soldiers serving in Iraq, Afghanistan or South America. In most cases, the ulcer spontaneously resolves within several months, leaving a scar. The goals of therapy are to accelerate healing, decrease morbidity and decrease relapse. For New World CL, the goals also include decreasing the risk of local and mucosal dissemination. There are no FDA approved drugs for the treatment of CL. Topical therapies that have been used include paromomycin and intralesional antimony, or thermotherapy. Systemic therapies include IM or IV pentavalent antimony preparations (sodium stibogluconate and meglumine), IV amphotericin B, or an oral azole antifungal drug (ketoconazole, fluconazole).

In 1-10% of patients with New World CL, *Leishmania* disseminates from the skin to the naso-oropharyngeal mucosa, resulting in mucosal leishmaniasis and destruction of nasal and pharyngeal structures. Death may occur due to complicating aspiration pneumonia. ML is mainly caused by organisms in the subgenus *Viannia*. There are no FDA approved drugs for the treatment of ML. Therapies that have been used include pentavalent antimony preparations and amphotericin B.

2.2 Miltefosine

2.2.1 Microbiology

Miltefosine is an alkyllysophospholipid analogue with *in vitro* activity against the promastigote and amastigote stages of *Leishmania* species. *In vitro, L. donovani* is generally considered the most susceptible, and *L. braziliensis* and *L. major* the least susceptible. The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death. Miltefosine is transported into the cell via transport machinery that includes miltefosine transporter and protein complex located on the parasite plasma membrane. Intrinsic and acquired resistance has been described and may be due to reduced levels of the translocation machinery proteins.

2.2.2 Clinical Pharmacology

As miltefosine was originally developed as an anti-neoplastic drug, no pharmacokinetic (PK) studies were conducted in healthy subjects. There were no disease-oriented studies in patients with cancer or in patients with leishmaniasis that had human pharmacology variables as primary endpoints. The PK information for miltefosine was obtained from adult patients with VL and CL.

[2] World Health Organization survey 2007 to 2010 to update the epidemiology of leishmaniasis accessed at http://www.who.int/leishmaniasis/resources/Leishmaniasis_worldwide_epidemiological_and_drug_access_update.pdf

PK of miltefosine in adult patients with VL (Study 3109)

The PK parameters of miltefosine on Day 23 following administration of 4 different doses in adult patients with VL are summarized in Table 1 below.

Table 1: Mean (%CV) Pharmacokinetic Parameters for Miltefosine Following Oral Tablet Administration to Adult Patients with Visceral Leishmaniasis

	On Day 23			After last dose
	C_{max} (µg/mL)	T_{max}[a] (hr)	AUC_{tau}[b] (µg·hr/mL)	$t_{1/2}$ (hr)
50 mg/d (6 wks) (Group 1, N=9)	23.5 (30.8)	8 (2 - 24)	445 (28.1)	166.7 (34)
50 mg/d (1 wk) /100 mg/d (3 wks) (Group 2, N=10)	39.2 (47.6)	5 (2-12)	378 (37.4)	199.8 (65.4)
100 mg/d (4 wks) (Group 3, N=10)	66.2 (28.5)	7 (2-12)	636 (26.7)	154 (31.1)
100 mg/d (1 wk) / 150 mg/d (3 wks) (Group 4, N=10)	75.9 (17.6)	4 (2-8)	486 (18.1)	202.8 (28.9)

[a]: Median (range)

[b]: AUC from time 0 h to 24 h, 12 h, 12 h, and 8 h for Groups 1, 2, 3, and 4, respectively

Due to the long half-life of miltefosine (> 6 days), plasma trough concentrations did not appear to reach a steady state at the end of treatment on Day 23 (Figure 1).

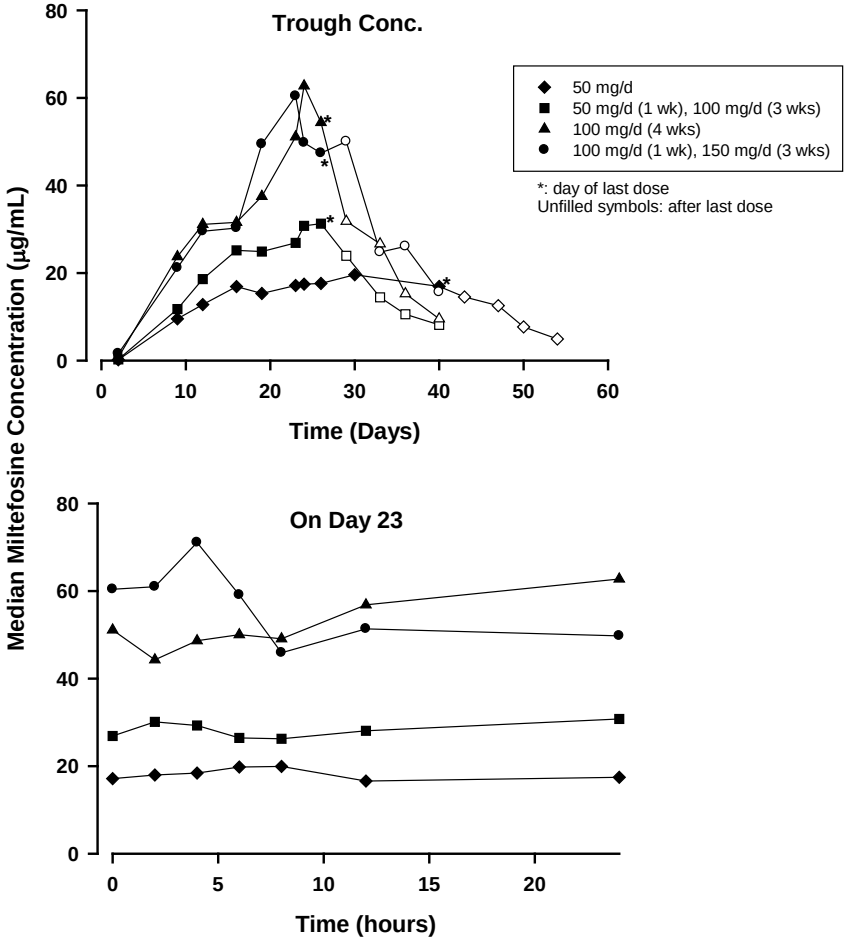

Figure 1: Median plasma concentrations of miltefosine following multiple oral administrations in patients with VL (Dose Groups 1 to 4, Study 3109). The upper panel shows drug concentrations before the first dose on each day and the lower panel shows drug concentrations on Day 23

PK of miltefosine in adult patients with CL (Dutch PK Study)

A population PK analysis was conducted with plasma concentrations obtained following administration of 50 mg TID (150 mg/day) for 28 days to adult patients with CL. Miltefosine PK during multiple dosing was best described by a 2-compartment, with first-order absorption, population model. The $t_{1/2\alpha}$ was 6.75 days from bootstrapping. C_{max} and AUC_{tau} were 37 µg/mL and 295 µg·hr/mL, respectively, based on simulated plasma concentrations after the last dosing on day 27. The apparent terminal $t_{1/2}$ was approximately 30 days and explains the fact that steady-state plasma concentrations were not achieved by 28 days of dosing.

Absorption

Absolute bioavailability has not been determined because intravenous miltefosine is hemolytic. In Study 3019, maximum concentrations following oral tablet administration were observed right before the next dose in many patients, indicating that the absorption of miltefosine may proceed throughout the dosing interval.

Distribution
No clinical studies provided the distribution characteristics of miltefosine. In rats, radioactivity of [^{14}C]miltefosine is widely distributed after both single and repeated oral administration. Human plasma protein binding of miltefosine, evaluated by an ultracentrifugation method, was 98% over the drug concentration range from 0.1 to 10 µg/mL.

Metabolism
Miltefosine is metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol, which is oxidized to palmitic acid. No oxidative metabolism of miltefosine was observed with any of the reconstituted cytochrome P450 (CYP) monooxygenase systems, comprising the following CYP enzymes: 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, 4A1.

Excretion
The urinary excretion of the unchanged drug on Day 23 after repeated oral administration of miltefosine to adult patients was below 0.2% of the daily dose.

Drug-Drug Interactions
Miltefosine is not a substrate, inhibitor, or inducer of CYP450 enzymes. Drug interaction studies have not been conducted.

Proposed dose and justification
The target regimen is 2.5 mg/kg/day for 28 consecutive days. Administration with food reduces gastrointestinal adverse reactions. The recommended dose regimen for miltefosine is based on the results of Study 3168 (placebo-controlled pivotal CL Trial) and Study 3154 (active-controlled pivotal VL trial). The recommended dosing regimen and number of 50 mg capsules per day determined by bodyweight is shown in Table 2.

Table 2: Proposed dosage and administration as a function of body weight

Weight	Dosage and Administration
30-44 kg	One 50 mg capsule twice daily with food (breakfast and dinner)
≥45 kg	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)

No exposure-response analysis was conducted in this NDA because there were limited PK data obtained in most of the clinical trials. Instead, the appropriate doses to be evaluated in the Phase 3 studies were determined based on the efficacy and safety observed in several dose-finding studies conducted by the sponsor.

2.2.3 Nonclinical Toxicology

The primary target organs for toxicity in the rat were kidney, GI tract (hyperplasia of stomach chief cells, hyperplasia and hypertrophy of intestinal mucosa), male reproductive organs (atrophy of testes, Leydig cell hyperplasia and adenomas, atrophy of prostate, epididymides, and seminal vesicles, spermatogenic granulomas in epididymides), female reproductive organs (ovarian

cysts, hydrometra, mucometra, and pyometra of the uterus, hyperplasia of cervical and vaginal mucosa) and the eye (corneal inflammatory changes, homogenization of the lens nucleus, swelling and vacuolization of lens fibers, and retinal degeneration). Dogs also experienced GI tract toxicity (vomiting, diarrhea, reduced food consumption, hyperemia of the intestinal mucosa) as well as specific toxicity to female reproductive organs (increased numbers of atretic follicles in the ovaries, cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus). Toxicities in both the GI tract and female reproductive organs were reversed during recovery in dogs.

A notable toxicity in rats but not in dogs was dose-dependent retinal degeneration. With sufficient duration of dosing, retinal degeneration was not fully reversible and was characterized by complete damage to photoreceptors inclusive of nuclei and the consecutive loss of inner retinal structures.

Formal carcinogenicity studies were not performed for miltefosine, but in a 52-week oral toxicity study in rats, tumors were observed at the high-dose of 21.5 mg/kg/day miltefosine (human equivalent dose (HED) of 3.44 mg/kg/day or roughly equal to the maximum recommended human dose (MRHD)). Tumors included: benign basal cell adenoma of the skin, multiple histiocytic sarcoma, squamous cell carcinoma in the uterus and malignant adenoacanthoma in the uterus that was observed in separate females (each in 1/30 females) and testicular Leydig cell adenoma observed in 3/30 males.

In a male fertility study in rats, miltefosine produced a dose-dependent impairment of the male reproductive system including reduced copulation index, dramatically reduced fertility, reduced sperm number and viability, increased morphologically altered sperm, and atrophied testes, prostate, and seminal vesicles. Testicular histopathology included slight to massive diffuse tubular atrophy with degenerative spermatocytes and spermatogonia. The NOAEL dose was considered to be 3.16 mg/kg (HED of 0.51 mg/kg/day or approximately 0.15 fold the MRHD). After a 10-week recovery period, the effects were reversed in rats receiving 8.25 mg/kg miltefosine, but most effects were not reversed in the rats receiving the high dose of 21.5 mg/kg.

Miltefosine also produced less pronounced effects on male reproductive organs in dogs. Testicular atrophy did not occur to a significant degree, but in a 52-week toxicology study, multifocal atrophy and degeneration of seminiferous tubules associated with focal mononuclear infiltrates was observed at an oral dose 6.19 mg/kg/day (HED of 3.34 mg/kg/day or approximately equal to the MRHD). Also in a 13-week toxicology study, dogs administered oral daily doses of ≥ 3.16 mg/kg/day (HED of 1.71 mg/kg/day or approximately 0.51 fold of the MRHD) experienced prostate atrophy. The prostate atrophy and seminiferous tubule degeneration were reversed during the recovery period.

In embryofetal studies in rats and rabbits, miltefosine doses ≥ 6.0 mg/kg caused pronounced fetal resorption in dams treated during the period of organogenesis. Miltefosine was a potent teratogen in rats when administered at doses of ≥1.2 mg/kg/day. Malformations included: undeveloped cerebrum, lumina of the skull filled with hemorrhagic fluid and in a few fetuses, further malformations including cleft palate and generalized edema. In rabbits, miltefosine doses of

≤ 2.4 mg/kg/day did not influence prenatal parameters (number of fetuses, number of resorptions, fetal and placental weights) increased variation rates, or cause malformations.

3 Clinical Trials

4 Visceral Leishmaniasis Indication

One study, Study 3154, was submitted in support of the VL indication. This study was conducted in 1999-2000 in Bihar, India. Data from another study, Study Z025, as published in the literature were submitted as supportive evidence[3]. This study was conducted in Ethiopia. In both countries, epidemiologically *L. donovani* is the causative species.

4.1 Study 3154

Study Design

This was a randomized, open-label, non-inferiority trial comparing oral miltefosine 2.5 mg/kg given daily for 28 days to amphotericin B deoxycholate 1 mg/kg every other day for 15 injections in the treatment of VL. Randomization ratio was 3 miltefosine: 1 amphotericin B. Amphotericin was chosen as the comparator drug instead of pentavalent antimony because resistance to antimony is prevalent in Bihar, India.

Subjects weighing less than 25 kg received miltefosine 50 mg orally once a day, and subjects weighing ≥ 25 kg received 50 mg orally twice a day. Amphotericin was administered intravenously over 6 hours every other day.

All subjects were hospitalized during treatment, and were monitored weekly until the end of therapy, and at six months after completion of therapy. Spleen or bone marrow aspiration was performed at screening and at end of therapy EOT (Day 28 for miltefosine group and Day 30 for amphotericin B group). A bone marrow or splenic aspiration was also performed for subjects who had signs or symptoms suggestive of VL relapse at the 6 month visit. All smears were read by the same pathologist, and one out of ten slides marked only with a code number was forwarded to an external pathologist for review under blinded conditions. Parasite density was scored microscopically from 0 (no amastigote per 1000 fields) to 6+ (> 100 amastigotes per field).

Sample size was calculated based on one-sided alpha 0.025, power 0.80 and NI margin of 15%, assuming final cure rates of 88 to 92% for miltefosine and 94 to 98% for amphotericin. Although the pre-specified NI margin was 15%, the FDA considered a margin of 10% more acceptable. (See Appendix 1 – NI margin justification).

[3] Ritmeijer, K. et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis 2006;43:357-364

Eligibility Criteria

Subjects ≥ 12 years of age with clinical signs and symptoms compatible with VL (fever, splenomegaly and cytopenia) confirmed by the presence of *Leishmania* amastigotes in spleen or bone marrow aspirates were eligible. Pregnant or lactating women and women unable to maintain contraception for the treatment period plus 2 months were excluded. Subjects with platelets < 50 x 10^9/L, WBC < 1 x 10^9/L, hemoglobin (Hb) < 6 g/100ml, Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) or alkaline phosphatase ≥ 3x upper limit of normal (ULN), bilirubin ≥ 2x ULN, creatinine or BUN ≥ 1.5x ULN or PT ≥ 5 seconds above control were excluded. Subjects who had undergone major surgery within the previous 2 weeks or had any uncontrolled condition, such as HIV infection, active tuberculosis, malaria or malignancy were also excluded, as were subjects who were receiving other concomitant anti-*Leishmania* drugs or had failed prior amphotericin B therapy.

Study Endpoints

Treatment response was classified as Initial Cure, Final Cure, Relapse or Failure. The primary efficacy endpoint was Final Cure.

Initial Cure was defined as absence of parasites at the EOT (parasite score 0 on spleen or bone marrow aspirates). Subjects with parasite density of 1 at EOT were re-assessed 1 month later, and designated as initial cure if the score was 0 or treatment failure if the score was > 0.

Final Cure was defined as Initial Cure plus absence of clinical signs and symptoms attributable to leishmaniasis during the 6 months follow up. Absence of clinical signs and symptoms attributable to VL was defined as:

1- Loss of fever that is attributed to VL and
2- Spleen size at least 30% smaller than at pre-treatment (only applicable if spleen size was > 1 cm below the costal margin at pre-treatment). If palpable spleen was ≤ 1 cm at pre-treatment, it must not be > 1 cm when clinical response is assessed, and
3- Hemoglobin ≥ 10.0 g/dl for female subjects or ≥ 11.5 g/dl for male subjects (or at EOT, residual decrement from the lower limit of normal < 10% of the decrement at baseline), and
4- Platelets ≥ 100,000/ul (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline), and
5- Leukocytes ≥ 3500/ul (or at EOT, residual decrement from the lower limit of normal < 30% of the decrement at baseline)

Subjects who had experienced initial cure but who did not have absence of clinical signs and symptoms of VL at the 6 months follow up visit were to undergo a repeat spleen or marrow aspiration. Those with a positive aspirate were classified as relapse.

Study Populations
The Intent-to-Treat (ITT) population included all subjects who received at least one dose of study medication. The Per Protocol (PP) population included the ITT subjects who were treated as planned and followed up for at least 6 months after EOT or until treatment failure. The Safety population included all subjects who were exposed to at least one dose of study medication.

Results

Subject Disposition

Subject disposition is shown in Table 3.

Table 3: Subject Disposition –Study 3154

	MLT	AMB
Screened	301	99
Randomized	301	99
ITT Population	299	99
Did Not Complete Treatment	9 (3.0%)	3 (3.0%)
Lack of tolerability/AE	4	2
"Intercurrent disease"	3	0
Withdrawal of consent	1	1
Death	1	0
Excluded from PP	12 (4.0%)	5 (5.0%)
Lack of tolerability/AE	4	2
"Intercurrent disease"	3	0
Withdrawal of consent	1	1
Death	2	0
Lost to Follow up	2	2
PP	287	94
Safety Population	299	99

Subject baseline characteristics are shown in Table 4

Table 4: Baseline Subject Characteristics – Study 3154

	MLT N = 299	AMB N = 99
Male*	211 (70.6%)	58 (58.6%)
Mean Age, years (SD)	26.5 (12.7)	26.3 (12.0)
Median Age, years (Range)	25.0 (12-64)	25.0 (12-60)
Age ≤ 17 years	102 (34.1%)	31 (31.3%)
Mean Weight. kg (SD)	38.6 (10.0)	38.3 (12.1)
Median Weight, kg (Range)	40.0 (15-67)	40.0 (14-64)
Mean BMI (SD)	16.1 (2.5)	16.3 (2.9)
Median BMI (Range)	15.9 (8.2-24)	16.4 (9.4-27.4)
Karnofsky score		
60	89 (29.8%)	31 (31.3%)
70	102 (34.1%)	32 (32.3%)
80	4 (1.3%)	1 (1.0%)
90	104 (34.8%)	35 (35.4%)
Newly diagnosed VL	214 (71.6%)	71 (71.7%)
Prior therapy**	85 (28.4%)	28 (28.3%)
Unresponsive	69	21
Relapse	16	7
Parasitology score		
1-10 per 1000 fields	130 (43.5%)	48 (48.5%)
1-10 per 100 fields	91 (30.4%)	25 (25.3%)
1-10 per 10 fields	53 (17.7%)	15 (15.2%)
1-10 per 1 field	22 (7.4%)	8 (8.1%)
10-100 per 1 field	3 (1.0%)	3 (3.0%)
Parasitology score		
Mean (SD)	1.9 (0.99)	1.9 (1.1)
Median (Range)	2 (1-5)	2 (1-5)
Median Duration of Fever	9.4 weeks	8.9 weeks
Splenomegaly, cm		
Mean (SD)	6.9 (4.3)	6.9 (4.3)
Range	0.5-27.0	1.0-21.0

*p = 0.035

**Pentavalent antimony

A statistically significant higher percentage of males were randomized to the miltefosine arm. The gender imbalance between the treatment arms was most noted at study site 1 (M/F ratio 4.2 in the miltefosine arm and 1.8 in the amphotericin arm), and to a lesser extent at study site 3 (M/F ratio 2.3 in the miltefosine arm and 1.1 in the amphotericin arm), but not at study site 2 (M/F ratio 1.6 in the miltefosine arm and 1.4 in the amphotericin arm).

Of note, the mean and median weight in each treatment arm was approximately 40 kg, the highest weight being 67 kg. This is lower than what would be expected for the US population.

Efficacy Analysis

The primary endpoint was final cure, defined as initial cure at EOT plus absence of signs and symptoms of VL at 6 months.

Table 5: Initial Cure – Study 3154

	Miltefosine N = 299	Amphotericin N = 99
Initial Cure	293 (98.0%)	97 (98.0%)
Parasitology score 0 at EOT	289 (96.7%)	96 (97.0%)
Parasitology score 1 at EOT	5 (1.7%)	1 (1.0%)

At 6 months follow up, 100 subjects did not have absence of signs and symptoms of VL as defined by the protocol: 88 miltefosine subjects (29.4%) and 12 (12.1%) amphotericin subjects. The investigators attributed these signs and symptoms to an alternative diagnosis in 73 subjects. The remaining 27 subjects, all in the miltefosine arm, underwent a splenic or marrow aspiration; nine were positive, indicating relapse. Final cure was 282/299 (94.3%) in the miltefosine arm and 96/99 (97.0%) in the amphotericin arm.

Table 6: Final Cure - Study 3154 – Sponsor Analysis

	Miltefosine N = 299	Amphotericin N = 99	Difference AMB-MLT
ITT			
Final Cure 95% CI	282 (94.3%) 91.1%, 96.7%	96 (97.0%) 91.4%, 99.4%	2.7% (-1.62%, 6.93%)
Relapse	9 (3.0%)	0	
Deaths	2 (0.7%)	0	
Not-assessable	6 (2.0%)	3 (3.0%)	
PP			
	Miltefosine N = 287	Amphotericin N = 94	Difference AMB-MLT
Final Cure	279 (97.2%)	94 (100%)	2.8% (0.88, 4.69%)

Of the 100 subjects without absence of signs and symptoms at 6 months, 27 were at study site 1, 35 at study site 2, and 38 at study site 3. However, of the 27 subjects who underwent a splenic or marrow aspirate at 6 months for parasitologic confirmation of cure or relapse, 23 were at site 1 (23/27, 85%), 2 were at site 2 (2/35, 5.7%) and 2 at site 3 (2/38, 5.3%). This indicates substantial inconsistency between the three site investigators in following up residual signs and symptoms at 6 months; the majority of subjects who did not have absence of VL signs and symptoms at 6 months at site 1 were further evaluated with a marrow or splenic aspirate, but a minority of subjects at sites 2 and 3 were further evaluated.

Because of this substantial inconsistency in following up subjects without absent signs and symptoms of VL at 6 months, the FDA reviewer evaluated the clinical data for these 100 subjects, blinded as to which subject underwent a splenic/bone marrow aspirate and judged that 27 subjects warranted further investigation. These included 9 subjects who had a positive aspirate, 4 subjects with a negative aspirate, and 14 additional subjects (12 in the miltefosine arm and 2 in the amphotericin arm). If these additional 14 subjects are conservatively considered

treatment failures/relapse, the final cure is estimated at 90.3% in the miltefosine arm and 94.9% in the amphotericin arm (treatment difference AMB-MLT, 4.6%, 95% CI -0.82%, 10.1%).

Final cure was similar in newly diagnosed subjects and in subjects who had previously failed antimony therapy. Final cure was lower in subjects who received less than 2-2.5 mg/kg miltefosine dose, a consideration given the anticipated higher weight of US patients.

Table 7: Final Cure by Miltefosine Dose – Study 3154 – Sponsor Cure Rates

Miltefosine Dose mg/kg	Final Cure	Relapse
1.7 -< 2	24/26 (92.3%)	1/26 (3.8%)
2- <2.5	96/104 (92.3%)	6/104 (5.8%)
2.5-< 3	114/121 (94.2%)	2/121 (1.7%)
3-3.9	39/39 (100%)	0
≥ 4	9/9 (100%)	0
Total	282/299 (94.3%)	9/299 (3.0%)

Table 8: Final Cure by Miltefosine Dose – Study 3154 – FDA Cure Rates

Miltefosine Dose mg/kg	Final Cure	Relapse
1.7- < 2	22/26 (84.6%)	3/26 (11.5%)
2- <2.5	92/104 (88.5%)	10/104 (9.6%)
2.5-< 3	109/121 (90.1%)	7/121 (5.8%)
3-3.9	38/39 (97.4%)	1 (2.6%)
≥ 4	9/9 (100%)	0
Total	270/299 (90.3%)	21/299 (7.0%)

All the documented relapses occurred in the miltefosine arm, raising concerns regarding development of resistance among the relapsed *Leishmania* species, and concerns regarding spread of resistance with widespread use.

Development of resistance has been explored in recently published literature. Prajapati et al.[4] compared *Leishmania* isolates from Bihar, India where miltefosine use is extensive, to isolates from Uttar Pradesh, India where miltefosine use is not extensive. Miltefosine IC_{90} was statistically significantly higher in Bihar compared to Uttar Pradesh. Bhandari et al. [5] reported significantly higher post-therapy IC_{50} compared to pre-therapy IC_{50} in VL patients who relapsed. Sundar et al. [6] reported increasing relapse rate of miltefosine in the treatment of VL in India after a decade of use. Similarly, Rijal et al. [7] reported increased relapse rate in VL patients treated in Nepal.

[4] Prajapati VK et al. In vitro antileishmanial drug susceptibility of clinical isolates from patients with Indian visceral leishmaniasis – status of newly introduced drugs. Am J Trop Med Hyg 2012;87:655-657

[5] Drug susceptibility in Leishmania isolates following miltefosine therapy in cases of visceral leishmaniasis and post kala-azar dermal leishmaniasis. PLoS Neglected Tropical Diseases 2012;6:e1657-

[6] Sundar S, Singh A., et al. Efficacy of miltefosine in the treatment of visceral leishmaniasis in India after a decade of use. CID 2012;55(4)543-50

[7] Rijal S, Ostyn B, et al. Increasing failure of miltefosine in the treatment of Kala-azar in Nepal and the potential role of parasite drug resistance, reinfection, or noncompliance. CID 2013;56:1530-8

4.2 Study Z025

Study Design and Endpoints

This study was conducted in 2003-2005 by Medicins Sans Frontieres in a semi-nomadic population in Ethiopia, where epidemiologically *L. donovani* is known to be the infecting species. The sponsor was unable to obtain the primary efficacy data for this study. The sponsor's study report and our analyses both used the published article that reported the findings of this study[3].

Z025 was a randomized, open-label study comparing oral miltefosine 100 mg daily for 28 days to IM sodium stibogluconate (SSG) 20 mg/kg daily for 30 days. Only male subjects ≥15 years of age were enrolled, because birth control in women could not be assured. Subjects with fever > 2 weeks duration and evidence of splenomegaly or lymphadenopathy and wasting and a negative malaria smear were eligible. VL was diagnosed by a high *Leishmania* direct agglutination test titer. Subjects with an indeterminate titer and subjects previously treated for VL underwent spleen or lymph node aspirate for parasitologic diagnosis. Spleen or lymph node aspirates were performed at end of therapy. Subjects who did not respond clinically or parasitologically to miltefosine were re-treated with SSG. Subjects who did not respond to SSG or were intolerant of SSG were re-treated with amphotericin B. The primary endpoint was final cure, defined as initial cure and no symptoms of relapse at 6 months. Initial cure was defined as a negative aspirate at EOT with clinical improvement, or if an aspirate could not be performed, as clinical cure.

The sponsor proposed a post-hoc primary endpoint of mortality by the end of therapy. This post-hoc primary efficacy endpoint was not considered acceptable because as discussed below, it is most likely more reflective of the toxicity of SSG rather than the efficacy of miltefosine. Additionally, without patient level data on all subjects we were not able to verify the study results completely. We will focus on the endpoint of final cure that is traditionally used in VL treatment studies.

Efficacy Results

290 subjects received miltefosine and 290 subjects received SSG. Subjects were matched as to age, BMI, hemoglobin, spleen size and ability to walk unaided. HIV serology testing was voluntary and typically done 2-3 weeks after providing consent to be in the study. Sixty-five percent of enrolled subjects underwent voluntary HIV testing, and approximately 30% of those tested were infected. A higher percentage of miltefosine subjects were HIV infected (22% vs. 15%), while a higher percentage of SSG subjects had unknown HIV status (38% vs. 33%).

Approximately 88% of subjects experienced initial cure at end of therapy in each arm. Although initial cure rates at EOT were similar, lack of initial cure among SSG recipients was driven by mortality while lack of initial cure among miltefosine subjects was driven by parasitologic or clinical failure. Of note, data from East Africa indicates that SSG therapy in HIV negative VL patients remains highly effective. The relatively high mortality in the SSG arm in this study is unlikely to be due to resistance/ineffective therapy and is more likely reflective of SSG toxicity.

Twenty-three miltefosine subjects who experienced initial failure were re-treated with SSG, while two SSG subjects who experienced initial failure were re-treated with amphotericin B. These subjects were not excluded from calculation of final cure, and it was unclear how many contributed to the final cure rate. Approximately 20% of subjects were lost to follow up in each arm. At 6 months, a higher percentage of miltefosine subjects relapsed. Final cure in the ITT population was 60% for miltefosine and 65.2% for SSG (MLT-SSG treatment difference -5.2%, 95 % CI, -13.0, 2.7). In the PP population, final cure rates were 79.5% for miltefosine and 82.2% for SSG (MLT-SSG treatment difference -2.7%, 95% CI -10.0%, 4.6%). However, including subjects who had initial failure and who received re-treatment in the final analysis of cure confounds the interpretation of final cure, especially in the miltefosine arm.

Table 9: Cure Rates – Study Z025

	MLT N = 290	SSG N = 290	Difference MLT-SSG 95% C.I.
Initial Cure	256 (88.3%)	254 (87.6%)	
No Initial Cure Death Clinical Failure	29 (10.0%) 6 (2.1%) 23 (7.9%)	30 (10.4%) 28 (9.7%) 2 (0.7%)	
Followed at 6 months	213 (73.5%)	202 (69.7%)	
Final Cure 95% CI	174 (60.0%) (54.1%–65.7%)	189 (65.2%) (59.4%–70.6%)	-5.2% (-13.0, 2.7)
Died During Follow up	11 (3.8%)	6 (2.1%)	
Total Deaths	17 (5.9%)	34 (11.7%)	
Relapse	30 (10.3%)	7 (2.4%)	

This study was considered supportive for many reasons: the primary data were not available for review, the final cure rate in the miltefosine arm was confounded by including subjects with initial failure who were re-treated in the final cure analysis, there was a relatively high rate of loss to follow up, and the population had a high prevalence of HIV co-infection.

4.3 Post Marketing Studies – VL

The sponsor submitted study report summaries for two post-marketing studies, Z013 and Z013b. Study Z013 was conducted in India and enrolled 1132 subjects, 704 adults and 428 children (< 12 years of age). Study Z013b was conducted in Nepal and enrolled 125 subjects, 33 children and 92 adults. Children 2-11 years of age received 2.5 mg/kg/day. Subjects ≥ 12 years of age and weighing < 25 kg received 50 mg daily for 28 days. Subjects ≥ 12 years of age and weighing ≥ 25 kg received 100 mg daily for 28 days. Definitions of clinical response were similar to Study 3154.

Table 10: Summary Results of Post Marketing VL Studies Z013 and Z013b

	Study Z013	Study Z013b
Enrolled	1132	125
Initial Cure	1055 (93.2%)	121 (96.8%)
Initial Failure	6 (0.6%)	1 (0.8%)
Returned for 6 month follow up	971 (85.8%)	117 (93.6%)
Relapse	44 (4.0%)	12 (9.6%)
Final Cure ITT	927/1132 (81.9%)	105/125 (94.0%)
Final Cure Evaluable	922/971 (95.5%)	105/117 (89.7%)
Deaths	3 (0.3%)	2 (1.6%)

5 Cutaneous Leishmaniasis (CL) Indication

In support of the CL indication, data from one pivotal trial (Study 3168) and 2 supportive trials (Study Z020 and Study Soto) were submitted.

5.1 Study 3168

Study Design

Study 3168 was a randomized, placebo-controlled trial conducted in 2000-2002 at two study centers, one each in Colombia and Guatemala.

Eligibility Criteria

Males and females ≥ 12 years of age with parasitologically confirmed CL in at least one lesion of ≥ 50 mm^2 area and without mucosal involvement were randomized in a 2:1 ratio to receive oral miltefosine or matching placebo for 28 days. Subjects weighing ≥ 45 kg received miltefosine 50 mg or matching placebo three times a day, while subjects weighing < 45 kg received miltefosine 50 mg or matching placebo twice a day.

Subjects with abnormal laboratory findings including platelet count <100 x 10^9/L, leukocyte count <3 x 10^9/L, hemoglobin <10 g/100 mL, AST, ALT or alkaline phosphatase >2 x ULN, bilirubin >1.5 x ULN, creatinine or BUN >1.5 x ULN, and subjects with any non-compensated or uncontrolled medical condition (such as active tuberculosis, malignant disease, severe malaria,

HIV, or other major infectious diseases) were excluded. Pregnant or lactating women and women of childbearing potential who were unable to comply with contraception during therapy and for 2 months after EOT were excluded. Subjects receiving, or having received anti-leishmania drugs within the preceding 4 weeks were also excluded.

Study Endpoints

Clinical response was defined as apparent cure, partial cure, definite cure or failure. The primary endpoint was apparent or partial cure at 2 weeks followed by definite cure at 6 months.

Apparent cure: Complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions at 2 weeks after EOT.

Partial cure: Incomplete epithelialization or incomplete regression of inflammatory induration of any lesion, no ≥ 50% enlargement of previously documented lesions, and absence of parasites, and no appearance of new lesions at 2 weeks after EOT. If parasitology was not done 2 weeks after EOT, the evaluation of partial cure was based on clinical parameters only.

Definite cure: Complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions at 6 months. In addition, in the interim period of 2 weeks and 6 months post-therapy, no positive parasitology should be documented, and no new lesions or enlargement of already existing lesions by > 50% should have occurred. .

Failure: Lack of achieving partial response (i.e., residual lesions with presence of parasites or appearance of new lesions or ≥ 50% enlargement of previously documented lesions) at 2 weeks

Subjects classified as failure at 2 weeks were also classified as failure at 6 months.

Study Populations

The primary analysis population was the intent-to-treat population (ITT) which included all subjects who received at least one dose of trial medication. The per-protocol (PP) population included all ITT subjects who received the trial medication for at least 90% of the planned treatment days and who were assessed for apparent cure.

Subject Disposition

Subject disposition in this study is summarized in Table 11.

Table 11: Subject Disposition – Study 3168

	Placebo	Miltefosine
Enrolled	44	89
ITT Population	44	89
Excluded From PP	2 (4.5%)	4 (4.5%)
Lost to follow up	1	2
Lost study medication	1	0
Due to non-compliance	0	1
Due to lack of tolerability	0	1
PP Population	42	85
Safety Population	44	89

Demographics

Subject demographics and disease characteristics are summarized in Table 12.

Table 12: Baseline Demographics and Disease Characteristics – Study 3168

	Placebo N = 44	Miltefosine N = 89
Male	38 (86.4%)	81 (91.0%)
Age (years)		
Mean (SD)	26.1 (12.6)	24.9 (9.8)
Range	12-63	12-55
Age < 18 years	14 (31.8%)	19 (21.3%)
Weight (kg)		
Mean (SD)	58.4 (11.3)	59.5 (11.0)
Range	33-82	29-84
BMI		
Mean (SD)	22.0 (3.0)	22.1 (2.9)
Range	16-29.8	14.6-35
Ethnicity		
Hispanic	32 (72.7%)	64 (71.9%)
Previous treatment for CL	10 (22.7%)	14 (15.7%)
Diagnosis of CL		
New	34 (77.3%)	77 (86.5%)
Unresponsive to prior therapy	3 (6.8%)	5 (5.6%)
Relapse	7 (15.9%)	7 (7.9%)
More than one lesion	16 (33.4%)	35 (29.3%)
Lesion Infiltration size (mm^2)		
Mean (SD)	854 (747)	603 (704)
Median	779	480
Range	36-4800	48-11360

Efficacy Results

Miltefosine was superior to placebo for the primary endpoint of partial and apparent cure at 2 weeks followed by definite cure at 6 months.

Table 13: Miltefosine Efficacy – CL – Study 3168

	Placebo N = 44	Miltefosine N = 89	Difference MLT-PLA 95% CI	P value
Definite Cure - ITT	13/44 (29.6%)	59/89 (66.3%)	36.7% (20.1, 53.4)	< 0.0001
Definite Cure - PP	13/42 (31.0%)	59/85 (69.4%)	38.4% (21.4, 55.5)	< 0.0001

Definite cure was similar in subjects who had received prior therapy and subjects with newly diagnosed disease.

Definite cure in Colombia was higher than definite cure in Guatemala in both the placebo and treatment arms, but miltefosine had a higher cure rate than placebo at each study center.

Table 14: Definite Cure by Study Center – Study 3168

	Placebo	Miltefosine	Difference	P value
	ITT			
Colombia	9/24 (37.5%)	40/49 (81.6%)	44.1%	
Guatemala	4/20 (20.0%)	19/40 (47.5%)	27.5%	
Total	13/44 (29.6%)	59/89 (66.3%)	36.7%	< 0.0001
	PP			
Colombia	9/24 (37.5%)	40/47 (85.1%)	47.6%	
Guatemala	4/18 (22.2%)	19/38 (50.0%)	27.8%	
Total	13/42 (31.0%)	59/85 (69.4%)	38.4%	< 0.0001

A possible explanation for the lower response rates in both study arms in Guatemala compared to Colombia may be related to differences in the prevalent epidemiologic species in each country. Epidemiologically, *L. braziliensis* is the causative agent in approximately 30% of CL lesions in Colombia and approximately 75% of CL lesions in Guatemala. *L. braziliensis* causes more protracted disease compared to other species: spontaneous resolution at 6 months of CL lesions caused by *L. braziliensis* is 6-8% compared to 30-38% for *L. panamensis* or to 68% for *L. mexicana*. Some strains of *L. braziliensis* may also be intrinsically less sensitive to miltefosine compared to the other species that could be due to low expression of the translocation machinery required to internalize the drug.

Definite cure rates were lower in subjects who received a miltefosine dose less than 2 mg/kg/day.

5.2 Study Z020

Study Z020 was split into two studies, Z020a and Z020b, and conducted in 2007-2009. Study Z020a was conducted in an area of Brazil where *L. guyanensis* is epidemiologically the predominant pathogen, while Z020b was conducted in an area of Brazil where *L. braziliensis* is epidemiologically the predominant pathogen.

Both studies were randomized, open-label, comparative trials that enrolled children 2-11 years of age and adults ≥ 12 years of age. Subjects with parasitologically confirmed CL received either miltefosine at a target dose of 2.5 mg/kg/day for 28 days or meglumine IM at 20 mg/kg/day for 21 days. The primary endpoint was definite cure, defined as complete re-epithelialization of all initial ulcers at 2 months and at 6 months and no new lesions and no residual lesions with parasites or ≥ 50% enlargement of a lesion prior to 6 months. There was no pre-specified statistical hypothesis.

This study was considered supportive due to the lack of statistical hypotheses, the small size of the study, and the lack of a justified NI margin. Additionally, there was limited information on early withdrawals from the study along with an imbalance of withdrawals across arms. However, we do believe that this study offers valuable information because it provides parasitologic data.

In each study, 40 adults and 20 children received miltefosine and 20 adults and 10 children received meglumine. In contrast to the other studies submitted for the NDA review, parasitologic speciation of the infecting *Leishmania* organisms was obtained in every subject. Since the applicant is limiting the indication to adult subjects, we are reporting only the results from those ≥ 12 years of age.

Subject Disposition

Table 15: Subject Disposition and Baseline Disease Characteristics – Subjects ≥ 12 years of Age – Z020

	Z020a		Z020b	
	Miltefosine	Meglumine	Miltefosine	Meglumine
Randomized/ITT	40	20	40	20
"Early Withdrawal"	4 (10.0%)	3 (15.0%)	4 (10.0%)	9 (45.0%)
Male	32 (80.0%)	17 (85.0%)	31 (77.5%)	11 (55.0%)
Mean Age –yrs (SD)	30.9 (13.5)	30.6 (14.6)	29.4 (14.2)	29.5 (13.4)
Age 12-17 years	8 (20.0%)	2 (10.0%)	6 (15.0%)	4 (20.0%)
Age ≥ 18	32 (80.0%)	18 (90.0%)	34 (85.0%)	16 (80.0%)
Mean Weight- kg (SD)	66.3 (13.5)	64.8 (11.3)	56.3 (10.2)	60.6 (11.8)
Subjects with one lesion	19 (47.5%)	8 (40%)	29 (72.5%)	19 (95.0%)
Subjects with more than one lesion	21 (53.5%)	12 (60.0%)	11 (27.5%)	1 (5.0%)
Mean N of lesions per subject	2.2 (1.3)	2.3 (1.4)	1.4 (0.7)	1.1 (0.5)
Mean Ulcer area per lesion	191 (200)	242 (236)	414 (349)	432 (309)
Mean Ulcer area per subject	425 (364)	569 (425)	570 (337)	476 (291)
*L. guyanensis**	39 (97.5%)	19 (95.0%)	0	0
*L. braziliensis**	1 (2.5%)	0	40 (100%)	20 (100%)

*Species identified by PCR. However, the details of the method and performance characteristics of the assay used were not available for review.

A higher percentage of meglumine subjects were withdrawn from Study Z020b early. The reasons for early withdrawal were not specified. Subjects who withdrew early were classified as failure. For the purposes of this document, the efficacy results lists failure of clinical response separately from failure because of early withdrawal.

Efficacy Results

Definite cure rates are shown in Table 16.

Table 16: Miltefosine Efficacy – Study Z020

	Z020a		Z020b	
	Miltefosine N = 40	Meglumine N = 20	Miltefosine N = 40	Meglumine N = 20
Definite Cure – ITT*	27 (67.5%)	12 (60.0%)	34 (85.0%)	9 (45.0%)
Failure	9 (21.5%)	5 (25.0%)	2 (5.0%)	2 (10.0%)
Early Withdrawal	4 (10.0%)	3 (15.0%)	4 (10.0%)	9 (45.0%)

* 95% CI of difference of Mil – Meg for Z020A (-18%, 33%), for Z020B (16%, 64%)

Definite cure rate was lower in subjects who received a miltefosine dose less than 2 mg/kg/day.

5.3 Study Soto

This was an investigator-initiated, open-label comparative study conducted in 2005-2007 in Bolivia where epidemiologically *L. braziliensis* is expected to be the predominant species.

Subjects ≥ 12 years of age were assigned to receive either oral miltefosine 2.5 mg/kg/day for 28 days or IM meglumine for 20mg/kg/d for 20 days in a 2:1 ratio. The primary efficacy endpoint was definite cure, defined as complete re-epithelialization of all lesions at 6 months after EOT. A lesion was defined as failure if it did not completely re-epithelialize at 6 months after EOT, or if the lesion enlarged by 50% at EOT or 1 month after EOT, if the lesion area did not diminish by 50% at 3 months after EOT, or the lesion relapsed. There was no pre-specified statistical hypothesis.

This open label study is viewed as supportive. In our assessment of the study, we had concerns over whether or not this study was truly randomized based on the timing of the initiation of treatment. There was no information as to why the study was stopped prior to reaching the full planned enrollment, there was a lack of a pre-specified statistical analysis plan, and there was no justified NI margin. Additionally, it appeared that three of the four control subjects who are listed as being lost to follow-up and imputed as failures in the primary analysis were likely not followed due to the closing of the study (these subjects are excluded from our analysis) and three miltefosine subjects whose information, including case report forms, were lost were not included in the study report or in any analysis, including that given below.

Efficacy Results

Forty three subjects received miltefosine. The information on three subjects was lost, and as mentioned, these were not included in the analysis. Eighteen subjects received meglumine, and as already mentioned we excluded three from the analysis. Subjects were matched as to age, gender, weight, number of lesions and lesion area. Definite cure occurred in 80% of miltefosine recipients and 86.7% of meglumine recipients.

Table 17: Miltefosine Efficacy – Study Soto

	Miltefosine N = 40	Meglumine N = 15	Difference MLT-MEG	95% CI
Definite Cure (%) 95% CI	32 (80.0%) 64.3%, 90.9%	13 (86.7%) 49.1%, 87.5%	-6.7%	(-26.3, 21.4)
Failure	6 (15.0%)	1 (6.7%)	+8.3%	
Lost to follow up	2 (5.0%)	1 (6.7%)	-1.7%	

5.4 Efficacy by Geographic Region

Parasitology data were only available for Study Z020. As epidemiologically expected, *L. guyanensis* was isolated in 99% of subjects in Manaus Brazil (Z020a), and *L. braziliensis* was isolated in 100% of adult subjects in Bahia, Brazil (Z020b). Parasitologic data were not

available for Study 3168 (Guatemala and Colombia) or Study Soto (Bolivia). However, *L. braziliensis* is epidemiologically the prevalent species in Bolivia, accounting for approximately 90% of CL lesions, and is also the epidemiologically prevalent species in Guatemala, accounting for approximately 70-75% of CL lesions. Despite the limitations of Studies Z020b and Study Soto, definite cures in these studies were higher than definite cure in Guatemala, even after accounting for the earlier timepoint of assessment of failure in Study 3168. Regional variation in the sensitivity of *L. braziliensis* to miltefosine cannot be excluded.

Table 18: Miltefosine Efficacy by Region – CL Subjects ≥12 years of Age

	Miltefosine Definite Cure	Miltefosine Definite Cure**
Guatemala* (3168)	19/40 (47.5%)	23/40 (57.5%)
Bolivia (Soto) *	32/40 (80.0%)	
Bahia, Brazil* (Z020b)	34/40 (85.0%)	
Colombia	40/49 (81.6%)	
Manaus, Brazil (Z020a)	27/40 (67.5%)	

*L. braziliensis epidemiologically most prevalent
** If failure is at 3 months post therapy rather than at 2 weeks post-therapy

6 Mucosal Leishmaniasis Indication

6.1 Study Z022

Study Design and Endpoints

For the ML indication, one single arm study, Study Z022, was submitted. The study was conducted in 2004-2006 in Bolivia, where *L. braziliensis* is epidemiologically the predominant pathogen. A comparative study was planned, but the study site refused randomization to a comparator antimonial treatment arm because, in their experience, antimonials were ineffective. Subjects refused randomization to an IV amphotericin comparative arm because miltefosine is orally administered.

Subjects ≥ 18 years of age with a scar of previous CL and mucosal signs and symptoms compatible with ML (erythema, edema, infiltration, erosion of the nares and/or nasal septum and/or epiglottis, uvula or palate), and *Leishmania* seen in histopathologic examination of the lesion aspirates or isolated from cultures, OR positive Montenegro test and no previous treatment for ML (or if previously treated, treatment must have been at least 6 months prior to enrollment and symptoms must have progressed over the past 3 months) and no clinically significant lab abnormalities or abnormalities on physical exam other than the *Leishmania* related findings were enrolled. Women of childbearing potential had to agree to contraception for the duration of therapy and 2 months after therapy.

Subjects were followed at 2 weeks, 2 months, 6 months, 9 months and 12 months after EOT.

The ITT population included all randomized subjects. The PP population included subjects who had received at least 90% of the planned treatment days and who were assessed at 12 months (76 subjects). The primary efficacy endpoint was cure at 12 months, defined as ≥ 90% improvement in mucosal severity score at 12 months compared to baseline. The mucosal severity score

consisted of the sum of severity grades (0 to 3) for each of erythema, edema, infiltration and erosion at each of five anatomic sites (nasal skin, nasal mucosa, palate, pharynx, and larynx).

Efficacy Results

Seventy-nine adult subjects received a target miltefosine dose of 2.5 mg/kg/day (150 mg/day) for 28 days. Baseline mucosal severity score ranged between 1 and 38, with a mean score of 10 (SD 8.2).

62% of ITT subjects were cured, with a severity score of 0 at 12 months, indicating complete healing.

Table 19: Miltefosine Efficacy – ML

	ITT N = 79	PP N = 76
Cured	49 (62.0%)	49 (64.5%)
Improved	16 (20.3%)	16 (21.1%)
No Change	6 (7.6%)	6 (7.9%)
Worsened	1 (1.3%)	1 (1.3%)
Presumptive Failure	4 (5.1%)	4 (5.3%)
Not Evaluable	3 (3.8%)	0

Because this is a single arm study, additional studies that evaluated therapies for ML were reviewed for an estimate of historical cure rates.

The results of Z022 have been published[8]. Although not included in the study report, the published article reported clinical response of 19 historical control subjects treated with amphotericin B deoxycholate at the same study center. The mean mucosal severity score at baseline was 10 (SD 5, range 5-23), comparable to that in the miltefosine subjects. Of the 19 amphotericin subjects, 3 discontinued the drug due to an adverse event and 2 were lost to follow up. 7 of the 14 evaluable subjects were cured (50.0%). The cure rate in the ITT population was 7/19 (36.8%).

In a study in patients with ML in Peru[9], 10/20 (50%) enrolled subjects who received 28 days of antimony treatment had resolution of ulcers 12 months later (10/16 (63%) in evaluable subjects,) compared to 12/20 (60%) enrolled subjects who received 42 days of antimony (- 12/19 (63%) in evaluable subjects,). In another study from Peru[10], a total of 81 subjects with ML were enrolled to receive sodium stibogluconate (SSG) with or without allopurinol. Eleven subjects withdrew because of adverse events. Thirty-seven subjects had sustained clinical cure at 12 months (cure rate 45.7% in ITT, and 52.8% in the evaluable population).

[8] Soto J. et al. Treatment of Bolivian Mucosal Leishmaniasis with Miltefosine. Clin Infect Dis 2007;44:350-6

[9] Franke E, Llanos-Cuentas A, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate in the treatment of mucosal leishmaniasis. Am J Trop Med Hyg 1994;51:77-82

[10] Llanos-Cuentas A et al. Efficacy of sodium stibogluconate alone and in combination with all allopurinol for the treatment of mucosal leishmaniasis. Clin Infect Dis 1997; 25: 677-684

In a study from Brazil[11], 11 subjects with ML received SSG plus oral pentoxifylline and 12 subjects received SSG plus placebo. One hundred percent of subjects had healing of all lesions at one year. Another study from Brazil[12] reported a cohort of 140 patients with ML treated with meglumine, pentamidine, amphotericin B or itraconazole. Healing of all lesions at one year occurred in 91% of meglumine subjects. Amphotericin treated patients had a cure rate of 82%.

Overall, the efficacy of miltefosine in the treatment of ML was numerically higher compared to amphotericin B in Bolivia. Efficacy of miltefosine was comparable to antimony in Peru, was lower compared to antimony or amphotericin in Brazil.

7 Safety

Safety signals of interest based on nonclinical studies are related to the kidney, liver, retina and reproductive organs. Miltefosine is also hemolytic when administered IV. Our evaluation of renal toxicity was based on elevations of Cr above baseline, whereas the sponsor's evaluation was based on elevations of Cr above ULN. For hepatic toxicity, the submitted datasets only allowed for assessment of transaminases and bilirubin at baseline, EOT and 6 months (VL study). Hence there are differences between the sponsor's and the FDA analysis. Safety results are summarized by indication.

7.1 VL Indication

The submitted database included primary data for 299 subjects who received at least one miltefosine dose in Study 3154, summary reports for dose-ranging studies in India that enrolled 349 subjects, summary reports for the two post-marketing studies Z013 and Z013b that enrolled a total of 1257 subjects, and periodic safety reports submitted to the German Regulatory Authorities. Primary safety data other than deaths were not submitted for Study Z025.

Drug Exposure – Study 3154

Two hundred ninety subjects (97%) received the full treatment duration of 28 days. The mean duration of exposure was 27.5 days. The mean and median doses were 2.6 and 2.5 mg/kg/day respectively.

Concomitant Medications – Study 3154

Eighty-two of 299 (27.4%) subjects in the miltefosine group and 93/99 (93.9%) in the amphotericin group received at least one concomitant medication. Analgesics and antihistamines were significantly more frequently administered to amphotericin recipients. The cited indication for the use of analgesics and antihistamines in the amphotericin arm was prevention of amphotericin infusion reaction.

[11] Machado PR, Lessa H et al. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. Clin Infect Dis 2007; 44:788-793

[12] Amato VS, Tuon FF et al. Mucosal leishmaniasis: description of case management approaches and analysis of risk factors for treatment failure in a cohort of 140 patients in Brazil. Journal of European Academy of Dermatology and Venereology 2009;23:1026-1034

Treatment Emergent Adverse Events – Study 3154

Table 20: Summary of AEs – Study 3154

	MLT N = 299	AMB N = 99
Subjects with at least one AE	125 (41.8%)	44 (44.5%)
Subjects with Serious AE	6 (2.0%)	1 (1.0%)
Subjects with AE leading to drug discontinuation	8 (2.7%)	3 (3.0%)
Death	2 (0.7%)	0

Spontaneously reported AEs occurred in a similar percentage of miltefosine and amphotericin subjects (Table 21). The sponsor elicited responses to the AEs of fever, rigors, vomiting and diarrhea. Vomiting and diarrhea were noted more frequently in miltefosine recipients, while rigors were noted in substantially higher percentage of amphotericin subjects. Fever occurred in a similar percentage of subjects, but was attributed to VL in miltefosine subjects and to amphotericin infusion reaction in amphotericin subjects (Table 22).

Table 21: Spontaneously Reported Adverse Events Noted in ≥ 2% of Subjects – Study 3154

System Organ Class	MLT N = 299	AMB N = 99
Blood and Lymphatics		
Thrombocytopenia	2 (0.7%)	2 (2.0%)
Gastrointestinal		
Diarrhea	9 (3.0%)	2 (2.0%)
Vomiting	3 (1.0%)	7 (7.1%)
General and Administration Site		
Asthenia	19 (6.3%)	4 (4.0%)
Pyrexia	28 (9.3%)	11 (11.1%)
Rigors	10 (3.3%)	1 (1.0%)
Metabolism and Nutrition		
Anorexia	69 (23.1%)	22 (22.2%)
Nervous System		
Headache	4 (1.4%)	2 (2.0%)
Respiratory and Thoracic		
Cough	8 (2.7%)	2 (2.0%)
Dyspnea	2 (0.7%)	2 (2.0%)

Table 22: Elicited AE – Study 3154

	MLT N = 299	AMB N = 99
Temperature ≥ 100^{o} F	254 (84.9%)	84 (84.8%)
Investigator-assessed as related to study drug	0	72 (72.7%)
Associated with rigors	1 (0.3%)	68 (68.7%)
Rigors	1 (0.3%)	90 (90.1%)
Vomiting	113 (37.8%)	20 (20.2%)
Diarrhea	61 (20.4%)	6 (6.1%)

Deaths, SAE and AE Leading to Drug Discontinuation

Two deaths occurred during the study, both in the miltefosine arm and both assessed as unlikely to be due to miltefosine. The first death occurred in a 13 year old male subject who became drowsy on Day 11 of miltefosine treatment after complaining of earache for 4 days. Physical exam and CSF evaluation were compatible with acute bacterial meningitis due to a Gram negative organism sensitive only to ciprofloxacin. He died 2 days later. The second death was a 15 year female who had finished the miltefosine course with fever resolution but persistent splenomegaly and severe anemia (Hb 3.9). Spleen aspirate was negative for *Leishmania* but positive for *P. vivax*. She was treated with chloroquine, followed by primaquine. She died three weeks after finishing the primaquine course (2 months after discontinuation of miltefosine). Her death was assessed as unlikely due to miltefosine.

Six miltefosine subjects and one amphotericin subject developed at least one SAE. Serious AEs that occurred in the miltefosine arm included the subjects with bacterial meningitis and malaria with fatal outcomes. The other SAEs included hemiplegia, hemiparesis, convulsions, Stevens-Johnson syndrome, melena and thrombocytopenia. SAEs in the amphotericin arm included renal impairment and nystagmus. Stevens-Johnson syndrome was assessed as related to miltefosine, melena and thrombocytopenia as possibly related and the other AEs as unrelated.

Eight miltefosine subjects and three amphotericin subjects developed an AE that led to drug discontinuation. These included the subjects with SAEs. The additional miltefosine subjects had skin rash and arthritis, CTC grade 4 diarrhea and grade 4 jaundice, all assessed as drug related. The additional amphotericin subjects had dyspnea and thrombocytopenia.

Renal Toxicity

Mean Cr increased from 0.9 to 1.1 among amphotericin recipients at EOT, but remained stable at 0.9 in the miltefosine arm. Mean Cr was similar in both arms at 6 months follow up. Absolute Cr values were between 2 and 5.5 in 6 subjects in each arm at EOT (2% vs. 6% in the miltefosine and amphotericin arms respectively), and did not exceed 2.1 at follow up in any subject.

All amphotericin subjects experienced some degree of Cr elevation above baseline at EOT, compared to approximately 50% of miltefosine subjects. In the miltefosine arm, a higher percentage of CTC grade 2 elevations occurred in subjects who received a dose > 2 mg/kg/day,

but grade1 elevations were not dose dependent. No miltefosine subject discontinued therapy due to renal impairment.

Table 23: Creatinine Elevations above Baseline – Study 3154

	MLT N = 299	AMB N = 99
EOT		
Cr 1-<1.5x baseline	120 (40.1%)	59 (59.6%)
Cr 1.5-<3x baseline	25 (8.4%)	40 (40.4%)
Cr ≥ 3x baseline	4 (1.3%)	0
6 Months Follow Up		
Cr 1-<1.5x baseline	93 (31.1%)	33 (33.3%)
Cr 1.5-<3x baseline	31 (10.3%)	10 (10.1%)
Cr ≥ 3x baseline	0	0

Table 24: Effect of Miltefosine Dose on Cr Elevation above Baseline – Study 3154

	Miltefosine Dose mg/kg			
	1.4-< 2 N = 26	2-<3 N = 225	≥3 N = 48	Total N = 299
Cr 1-<1.5x baseline	12 (46.2%)	90 (40.0%)	18 (37.5%)	120 (40.1%)
Cr 1.5-<3x baseline	1 (3.8%)	20 (8.9%)	4 (8.3%)	25 (8.4%)
Cr ≥ 3x baseline	0	4 (1.8%)	0	4 (1.3%)

Hepatic Toxicity

Mean transaminase values, mean alkaline phosphatase and mean bilirubin remained stable in each arm during therapy. A higher percentage of miltefosine subjects had elevations in transaminases and alkaline phosphatase at EOT. The majority were CTC grade 1. One miltefosine subject discontinued therapy due to isolated hyperbilirubinemia.

Table 25: Elevations of Liver Laboratory Parameters at EOT – Study 3154

EOT	MLT N = 299	AMB N = 99
ALT		
ALT >1-3x ULN	138 (46.2%)	31 (31.3%)
ALT >3-5x ULN	9 (3.0%)	1 (1.0%)
ALT > 5-20x ULN	0	1 (1.0)
ALT >20x ULN	0	0
AST*		
AST >1-3x ULN	256 (85.6%)	73 (73.7%)
AST 3-5 x ULN	51 (17.1%)	9 (9.1%)
AST > 5-20 x ULN	10 (3.3%)	2 (2.0%)
AST > 20 x ULN	0	0
Alkaline Phosphatase		
AP >1-2.5x ULN	31 (10.4%)	6 (6.1%)
AP > 2.5-5x ULN	3 (1.0%)	1 (1.0%)
AP >5xULN	0	0
Total Bilirubin		
Bilirubin ≥ 1.5 mg/dL	2 (0.7%)	1 (1.0%)

*38 subjects had multiple AST determinations at EOT with discordant results.

Hematologic Toxicity

Hemoglobin improved more rapidly during therapy in miltefosine recipients. A higher proportion of amphotericin recipients had Hb decrease of ≥ 2 gm at EOT. These findings likely reflect known amphotericin B hematologic toxicity. At 6 months follow up, a higher proportion of miltefosine recipients had decrease of Hb compared to baseline, likely reflecting the higher incidence of relapse.

Table 26: Mean Hematology Parameters – Study 3154

	MLT N = 299	AMB N = 99
Hemoglobin (Mean, SD)		
Screening	8 (1.6)	8.2 (1.8)
EOT	9.4 (2)	8.7 (1.6)
6 month FU	12 (1.9)	12.2 (1.4)
WBC (Mean, SD)		
Screening	3300 (1684)	3694 (1860)
EOT	6339 (3511)	6041 (2532)
6 month FU	8500 (2780)	9260 (2980)
% Neutrophils (Mean, SD)		
Screening	43 (13)	43 (12.4)
EOT	49 (13)	49 (14)
6 month FU	50 (12)	53 (14)
Platelets (Mean, SD)		
Screening	119 (67)	115 (50)
EOT	228 (125)	223 (114)
6 month FU	202 (76)	203 (70)

Table 27: Hb Decrease by ≥ 2 gm at EOT – Study 3154

Hb decrease ≥2 gm From Baseline	MLT N = 299	AMB N = 99
EOT	10 (3.3%)	8 (8.1%)
6 months FU	5 (1.7%)	0

Mean WBC increased similarly in miltefosine and amphotericin arms during therapy. A higher proportion of miltefosine subjects had WBC < lower limit of normal at EOT.

Table 28: Subjects with WBC < Lower Limit Normal (4000 cells/mm3)

	MLT N = 299	AMB N = 99
Screening		
WBC <4000 -3000	83 (27.8%)	25 (25.6%)
WBC <3000-2000	98 (32.8%)	26 (26.3%)
WBC <2000-1000	44 (14.7%)	9 (9.1%)
WBC <1000	1 (0.3%)	0
EOT		
WBC <4000 -3000	75 (25.1%)	33 (33.3%)
WBC <3000-2000	67 (22.4%)	10 (10.1%)
WBC <2000-1000	19 (6.4%)	2 (2.0%)
WBC <1000	0	0
6 months FU		
WBC <4000 -3000	3 (1.0%)	1 (1.0%)
WBC <3000-2000	2 (0.7%)	0
WBC <2000-1000	1 (0.3%)	0
WBC <1000	0	0

Mean platelet count increased similarly in both treatment arms, but a higher proportion of miltefosine subjects had platelet counts < 150,000 at EOT and at 6 months. The higher proportion of subjects with thrombocytopenia at 6 months likely reflects the higher incidence of relapse in the miltefosine arm, but the higher incidence of thrombocytopenia at EOT may indicate drug toxicity.

Table 29: Subjects with Thrombocytopenia – Study 3154

	MLT N = 299	AMB N = 99
Screening		
<150k – 75k	146 (48.8%)	60 (60.6%)
<75k-50k	71 (23.7%)	20 (20.2%)
<50k-25k	7 (2.3%)	1 (1.0%)
< 25k	2 (0.7%)	0
EOT		
<150k – 75k	145 (48.5%)	44 (44.4%)
<75k-50k	32 (10.7%)	8 (8.1%)
<50k-25k	5 (1.5%)	1 (1.0%)
< 25k	2 (0.7%)	1 (1.0%)
6 months FU		
<150k – 75k	74 (24.8%)	20 (20.2%)
<75k-50k	4 (1.3%)	1 (1.0%)
<50k-25k	2 (0.7%)	0
< 25k	0	0

Comorbidities in the 28 subjects who died in the SSG arm included pulmonary and extra-pulmonary tuberculosis, pneumonia, diarrhea, giardiasis, sepsis syndrome, renal failure, cardiogenic shock, malaria, pancreatitis and CNS toxoplasmosis. Two subjects died suddenly due to SSG cardiac toxicity, and six additional subjects died of unknown reasons. Comorbidities in the six subjects who died in the miltefosine arm included sepsis, tuberculosis and retroviral infection. Three subjects died of unknown reasons. The published article states that vomiting was more frequent in miltefosine recipients (55% vs. 32%), but more severe in SSG recipients: 9% of miltefosine recipients and 29% of SSG recipients had the drug withheld due to vomiting. One subject discontinued the drug due to rash.

7.2 VL Dose Ranging Studies

Adverse events reported in dose ranging studies conducted in India included nausea, vomiting, diarrhea, anorexia, elevations of liver enzymes and elevations of creatinine. Daily doses of 200 and 250 mg were poorly tolerated due to nausea and vomiting, and CTCAE Grade 3 liver and renal toxicities were noted at 200 mg daily dose. Two subjects died, one of pulmonary infection and one of renal and cardiac failure.

7.3 Post-Marketing VL Studies Z013 and Z013b

A total of 1257 subjects were enrolled in these two studies.

In Study Z013, nausea and vomiting were the most common AEs, reported in approximately 8% of subjects. Three subjects died in Study Z013 (mortality rate 0.3%): a 2 year old boy who presented with abdominal pain and swelling (no further details), and a 13 year old girl with history of bloody diarrhea for 4 months prior to VL diagnosis, and leukopenia/neutropenia and severe thrombocytopenia at initiation of miltefosine. She received broad spectrum antibacterial drugs and continued to experience bloody stools, then developed abdominal distention on day 4, and expired on day 8 after cardiopulmonary arrest. One subject died in a car accident. Serious AEs occurred in five subjects: volume depletion and increased Cr, and diarrhea with or without vomiting. Miltefosine was discontinued in two subjects due to an AE: generalized pruritic macular rash, and vomiting with volume depletion. CTCAE grade 1 elevation in ALT and AST occurred in 23% and 31% of subjects respectively, grade 2 elevations in 9% and 5% and grade 3 elevations in approximately 1%. CTCAE grade 1, 2 and 3 Cr elevations occurred in 14%, 1.6% and 0.6% of subjects respectively. Two pregnancies were reported, one with estimated date of conception 2 weeks after EOT and one with estimated date of conception 3 months after EOT. Both babies were healthy.

In Study Z013b, vomiting, diarrhea and abdominal pain were the most common AEs, respectively occurring in 43%, 25% and 17% of subjects. Two subjects died (mortality rate 1.6%): a 13 year old girl secondary to sepsis due to foot abscess and a 26 year old woman with BMI 13 who was also receiving metronidazole for concomitant *E. histolytica* infection. On day 4 of study treatment, she developed pedal edema. On Day 7, liver and renal function and ECG and

respiratory evaluations were normal. On day 9, she developed SOB and lost consciousness. She was taken to faith healer and died the same day. Both deaths were assessed as unrelated to miltefosine. One additional subject had SAEs of volume depletion and elevated creatinine. One pregnancy was reported with an estimated date of conception at week 2 of therapy. A healthy baby was delivered.

7.4 CL Indication

Patient level data was submitted for subjects enrolled in the placebo controlled study and the active controlled studies.

Drug Exposure

Two hundred nine subjects ≥ 12 years of age received at least one miltefosine dose in studies 3168, Soto and Z020. Fifty-eight subjects ≥ 12 years of age received meglumine and forty-four subjects received placebo. The mean miltefosine dose ranged between 2.3 and 2.6 mg/kg/day, and the median dose was 2.5 mg/kg/day. Duration of exposure ranged between 10-28 days, with a mean duration of 27.4 days.

Treatment Emergent Adverse Events

One miltefosine subject discontinued therapy due to an AE (motion sickness on Day 27 of treatment). There were no SAEs and no deaths.

The main adverse reactions noted more frequently in miltefosine recipients compared to placebo recipients were nausea, vomiting, diarrhea, headache, dizziness, somnolence, pruritus, asthenia, decreased appetite, pyrexia, infection at lesion site and lymphadenopathy/lymphangitis. Motion sickness was coded as an AE only at the Colombia site of Study 3168, the only study with a placebo arm, and thus erroneously appears as more frequent in the placebo arm. These subjects were also coded as experiencing headache and nausea individually.

Adverse events noted more frequently in miltefosine subjects ≥12 years of age compared to meglumine were abdominal pain, diarrhea, dyspepsia, nausea, vomiting, pyrexia, dizziness, somnolence, pruritus and lymphadenopathy/lymphangitis.

Table 30: Adverse Events Occurring in ≥ 2% of Subjects ≥ 12 years of age – Studies 3168, Soto and Z020

System Organ Class	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
Blood and Lymphatics			
Lymphadenopathy	4 (1.9%)	2 (3.4%)	0
Ear and Labyrinth			
Motion Sickness	26 (12.4%)	0	10 (22.7%)
Gastrointestinal			
Abdominal Pain	19 (9.1%)	3 (5.2%)	4 (9.1%)
Diarrhea	25 (12.0%)	3 (5.2%)	2 (4.5%)
Dyspepsia	12 (5.7%)	2 (3.4%)	3 (6.8%)
Nausea	82 (39.2%)	3 (5.2%)	5 (11.4%)
Vomiting	37 (17.7%)	0	0
General/Administration Site			
Application site	0	6 (10.3%)	0
Asthenia	8 (3.8%)	4 (6.9%)	0
Malaise	4 (1.9%)	1 (1.7%)	1 (2.3%)
Pain at lesion	18 (8.6%)	5 (8.6%)	0
Pyrexia	27 (12.9%)	6 (10.3%)	2 (4.5%)
Infections and Infestations			
Lymphangitis	7 (3.3%)	0	0
Lesion Infection	3 (1.4%)	2 (3.4%)	0
Parasitic	4 (1.9%)	0	1 (2.3%)
Metabolism and Nutrition			
Decreased appetite	13 (6.2%)	4 (5.8%)	0
Musculoskeletal			
Arthralgia	7 (3.3%)	23 (39.7%)	1 (2.3%)
Back pain	6 (2.9%)	1 (1.7%)	0
Myalgia	2 (1.0%)	7 (12.1%)	2 (4.5%)
Nervous System			
Dizziness	19 (9.1%)	4 (6.9%)	0
Headache	63 (30.1%)	20 (34.5%)	10 (22.7%)
Somnolence	5 (2.4%)	0	0
Skin and Subcutaneous Tissue			
Pruritus	11 (5.3%)	0	0
Rash	3 (1.4%)	2 (3.4%)	

Renal Toxicity

In all studies except Z020b, mean Cr increased in the miltefosine arm and remained stable in the comparator arm at EOT. Absolute Cr values were however < 2 mg/dl. Some degree of Cr elevation above baseline was noted at EOT in approximately 65% of miltefosine subjects compared to approximately 35% of meglumine subjects and 50% of placebo subjects. However, a greater percentage of miltefosine subjects had CTCAE grade 2 elevations (1.5-3 times above baseline). The percentage of miltefosine subjects with grade 2 elevations above baseline was

higher at doses greater than 2.2 mg/kg/day, but grade 1 increases were not dose dependent (Table 32).

Hepatic Toxicity

A similar proportion of miltefosine, meglumine and placebo subjects had elevations of liver enzymes above ULN at EOT.

Hematologic Toxicity

No hematologic toxicities were noted.

Table 31: Summary of Laboratory Changes – Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

EOT	Miltefosine N = 209	Meglumine N = 58	Placebo N = 44
Cr			
Cr >1-<1.5x baseline	99 (47.4%)	17 (29.3%)	24 (45.5%)
Cr 1.5-<3x baseline	36 (17.2%)	3 (5.1%)	2 (4.5%)
Cr 3-<6x baseline	2 (1.0%)	0	0
ALT			
ALT >1-3x ULN	13 (7.7%)	4 (6.9%)	2 (4.5%)
ALT >3-5x ULN	0	1 (1.7%)	0
AST			
AST > 1-3x ULN	7 (4.1%)	5 (8.6%)	1 (2.3%)
AST >3-5x ULN	0	1 (1.7%)	0
Alkaline Phosphatase			
AP >1-2.5x ULN	18 (10.7%)	3 (5.1%)	7 (15.9%)
AP >2.5-5x ULN	0	0	0
Total Bilirubin			
Bilirubin ≥1.5 mg/dL	1 (0.5%)	0	2 (4.5%)

Table 32: Effect of Miltefosine Dose on Cr at EOT – Subjects ≥ 12 years of Age – Studies 3168, Soto and Z020

Miltefosine				
EOT	1.4-2.2 N = 58	2.3-<3 N = 131	≥ 3 N = 20	Total N =209
Cr >1-<1.5x baseline	32 (55.2%)	62 (47.3%)	5 (25.0%)	99 (47.4%)
Cr ≥ 1.5-< 3 x baseline	7 (12.1%)	25 (19.1%)	4 (20.0%)	36 (17.7%)
Cr ≥ 3-6x baseline	1 (1.7%)	1 (0.8%)	0	2 (1.0%)
Total	40 (69.0%)	88 (67.2%)	9 (45.0%)	137 (65.6%)

7.5 ML Indication

Drug Exposure

Seventy-nine subjects received at least one miltefosine dose. The mean and median duration of exposure were 29 days and 28 days respectively. The mean and median doses were 2.6 mg/kg/day.

Treatment Emergent Adverse Events

Seventy-four subjects (94%) experienced at least one AE, and one subject died. The subject who died was a 26 year old woman who experienced CTC grade 1 nausea and vomiting on Days 9 and 13 of therapy, and suffered soft tissue trauma on Day 14 followed by abdominal pain, malaise, vomiting and transient rash. She was hospitalized on Day 16 and was noted to have fever, tachypnea, hypotension and severe RUQ pain. She remained in shock and had cardiopulmonary arrest the following day. Death was assessed as unlikely due to miltefosine.

Main adverse events noted in ≥ 2% of subjects included abdominal pain, dysphagia, gastritis, nausea, malaise, non-cardiac chest pain, pyrexia, decreased appetite, arthralgias, back pain, dizziness, headache, and pruritus.

Laboratory Changes

Mean Cr remained stable during therapy. At EOT, approximately 35% of subjects had some degree of Cr elevation above baseline, but most of these elevations were CTC grade 1 (< 1.5x baseline) and the highest absolute Cr value was < 1.5. No changes in liver enzymes, bilirubin or hematology parameters were noted.

7.6 Other Post-Marketing Safety

As of November 2011, approximately 100,000 miltefosine prescriptions have been dispensed. The German regulatory authorities updated the product labeling to include thrombocytopenia in 2008. Other serious unlisted AEs included one case of agranulocytosis, regional lymphadenopathy, seizures, migraine headache, epistaxis, gingival bleeding, scrotal pain, epididymal swelling and several reports of decreased ejaculate volume. No pregnancies other than the three already mentioned were reported.

7.7 Organ-Specific Toxicity

Reproductive Toxicity
In animal toxicology studies, miltefosine was associated with testicular atrophy and reduced fertility in male rats, follicular atresia in female dogs, and embryotoxicity and/or teratogenicity in pregnant female rats and rabbits.

Men

Spermiograms were obtained at screening, 2 weeks and 6 months in 15 men who participated in the CL study, Study 3168 (11 miltefosine recipients and 4 placebo recipients). There were large variations in sperm counts and motility. The results were judged as inconclusive.

Two hundred twenty male subjects who previously participated in Phase 2 VL studies and in Study 3154 in India and who had a female sexual partner were retrospectively tracked and queried regarding reproductive performance. These included 197 miltefosine recipients and 23 amphotericin recipients. Assessments were done 11-57 months after miltefosine therapy. 69% of miltefosine male recipients (136/197) had proven fertility documented by at least one delivery or ongoing pregnancy. 58% (56/96) of the subset of male subjects who were enrolled in Study 3154 had proven fertility compared to 52% (12/23) of amphotericin recipients.

Post treatment spermiograms were also obtained in 12 miltefosine subjects enrolled in Study 3154. In ten subjects, the findings were normal. One man had oligospermia but had generated two pregnancies since end of treatment with miltefosine. The other man was 35 years old and had not generated progeny at any age. The oligospermia in this patient was documented 3 years after end of treatment.

Four cases of testicular pain were reported in one of the CL studies (Study Z020a). Scrotal pain, decreased ejaculate volume or absent ejaculation during therapy have been reported post-marketing.

Women

A total of 143 women at least 12 years of age were enrolled in the premarketing clinical trials (3168, Soto, Z020, Z022 and 3154). All were required to use some form of birth control for the duration of treatment and for 2-3 months post therapy. No pregnancies were reported.

Three pregnancies were reported in the sponsored post-marketing studies Z013 and Z013b, all without congenital abnormalities.

As already mentioned, approximately 100,000 miltefosine prescriptions have been dispensed as of November 2011. Based on the male/female ratio of subjects enrolled in clinical trials, it is estimated that at least 20,000 women have received the drug, and it is expected that more than 3 pregnancies would have occurred, even if optimal birth control is used. It is likely that pregnancies are under-reported.

Retinal Toxicity

Retinal degeneration that was dose and duration dependent was noted in the 8 week and 52 week rat toxicity studies, but was not noted in the dog toxicity studies. Ophthalmologic evaluation in 25 cancer patients who received oral miltefosine in Germany in 1992 concluded that miltefosine may induce electrophysiologically detectable changes in the retinal pigment epithelium of the human eye without associated impairment of visual acuity or changes the electroretinogram.

All Phase 2 VL studies and Study 3154 in India included weekly visual assessment (total 548 subjects). Study 3168 in CL patients also included visual assessments. One subject was reported as having an unspecified “abnormal fundoscopy” in one eye that resolved at 6 months and one subject was reported as having “central retinosis”. Visual findings were otherwise unremarkable, and no visual symptoms were reported in any of the studies or post-marketing.

Cardiac Safety

The effects of miltefosine on the QT interval have not been rigorously evaluated. A thorough QT study was not conducted because the need for lengthy exposures to achieve steady state and the teratogenic effects and potential reproductive toxicity of miltefosine precluded conducting such a study in healthy volunteers, and ethical considerations precluded conducting a placebo-controlled QT study in patients with leishmaniasis. A dedicated QT study that links PK information to ECG changes in VL patients will be considered post-marketing.

Topics for Discussion

VL Indication

1. Has the applicant demonstrated the safety and effectiveness of miltefosine in the treatment of visceral leishmaniasis caused by *L. donovani*?
    a. If yes, are there any specific issues that should be addressed in labeling?
    b. If no, what additional data are needed?

CL Indication

1. Has the applicant demonstrated the safety and effectiveness of miltefosine in the treatment of cutaneous leishmaniasis caused by members of the subgenus *Viannia* (*L. braziliensis, L. guyanensis* and *L. panamensis*)?
    a. If yes, are there any specific issues that should be addressed in labeling?
    b. If no, what additional data are needed?

ML Indication

1. Has the applicant demonstrated the safety and effectiveness of miltefosine in the treatment of mucosal leishmaniasis?
    a. If yes, are there any specific issues that should be addressed in labeling?
    b. If no, what additional data are needed?

8 Appendix 1

8.1 Non-Inferiority Margin Justification for Study 3154

VL is thought to be fatal if untreated. There are no data regarding the placebo response rate for the endpoint of final cure (negative parasitology at EOT plus absence of s/s of VL at 6 months). Pentavalent antimony preparations have been the mainstay of therapy for decades, but resistance has led to abandonment of these agents in Bihar, India. Studies evaluating the efficacy of pentavalent antimony in Bihar were therefore used to conservatively estimate the placebo cure rate.

In India until the late 1970s, sodium stibogluconate (SSG) at 10 mg/kg IM (600 mg maximum) for 6 to 10 days was considered adequate to treat VL. When cure rates decreased to 84%, a WHO Expert Committee recommended increasing SSG doses to 20 mg/kg/day up to maximum of 850 mg for 20 day[13]. Because doses of SSG have been more uniform after that recommendation, the analysis was limited to reports published after 1988-1990 and that used a dose of 20 mg/kg/day for 30 days. All cited studies used the same definitions for initial and final cures. These trials were active controlled comparative trials, but only the results for the subjects enrolled in the SSG arm are shown in the table.

Table 33: Effectiveness of SSG in the Treatment of VL in Bihar, India

Citation	N	Initial Cure ITT	Final Cure ITT
Sundar[14] 1997	52	20/52 (38.5%)	18/52 (34.6%)
Thakur[15] 1998	80	48/80 (60%)	46/80 (57.5%)
Jha[16] 1998	30	19/30 (63.3%)	19/30 (63.3%)
Sundar[17] 2000	209	89/209 (42.5%)	73/209 (35%)
Thakur[18] 2000	50	27/50 (54.0%)	26/50 (52.0%)
Thakur[19] 2004	60	22/60 (36.6%)	28/60 (46.6%)
Das[20] 2005	182	89/182 (48.9%)	65/182 (35.7%)
Pooled Estimate 95% CI	663	48.2% (40.80%, 55.60%)	47.1% (38.14%, 56.03%)

[13] Croft SL., Sundar S., and Fairlamb A. Drug resistance in leishmaniasis. Clinical Microbiology Reviews 2006;18:111-126

[14] Sundar S., et al. Response to interferon-γ plus pentavalent antimony in Indian visceral leishmaniasis. JID 1997;176:1117-9

[15] Thakur CP., et al. Do the diminishing efficacy and increasing toxicity of sodium stibogluconate in the treatment of visceral leishmaniasis in Bihar, India, justify its continued use as a first line drug? An observational study of 80 cases. Ann Trop Med Parasitology 1998;92:561-569

[16] Jha TK., et al. Randomized controlled trial of aminosidine (paromomycin) vs. sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. BMJ 1998;316:1200-1204

[17] Sundar S., et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. CID 2000;31:1104-1107

[18] Thakur CP., et al. A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. Transactions of the Royal society of Tropical Medicine and Hygiene 2000;94:429-431

[19] Thakur CP., Narayan S. A comparative evaluation of amphotericin B and sodium antimony gluconate as first line drugs in the treatment of Indian visceral leishmaniasis. Annals Tropical Medicine and Parasitology 2004;98:129-138

[20] Das VNR., et al. Magnitude of unresponsiveness to sodium stibogluconate in the treatment of visceral leishmaniasis in Bihar. National Medical J of India 2005;18:131-133

Studies evaluating amphotericin B deoxycholate in the treatment of VL in India are summarized. These trials were active controlled comparative trials. Only the results for subjects who received amphotericin B deoxycholate are shown.

Table 34: Effectiveness of Amphotericin B in the Treatment of VL in Bihar, India

Citation	N	Initial Cure ITT	Final Cure ITT
Mishra[21] 1992	60	60/60 (100%)	59/60 (98%)
Mishra[22] 1994	40	40/40 (100%)	40/40 (100%)
Thakur[23] 1999	938	935/938 (99.7%)	931/938 (99.3%)
Sundar[24] 2004	51	49/51 (96%)	49/51 (96%)
Thakur[19] 2004	60	60/60 (100%)	60/60 (100%)
Sundar[25] 2007	4 AMB arms 245 244 500 496	 237/245 (96.7%) 229/244 (93.9%) 491/500 (98.2%) 482/496 (97.2%)	 234/245 (96%) 225/244 (92%) 483/500 (97%) 476/496 (96%)
Sundar[26] 2007*	165	164/165 (99.4%)	163/165 (99%)
Das[27] 2009	41	39/41 (95%)	38/41 (92%)
Sundar[28] 2010	108	106/108 (98.1%)	104/108 (96.3%)
Sundar[29] 2011	157	148/157 (94.3%)	146/157 (93%)
Pooled Estimate 95% CI	3105	98.5% (97.19%, 99.77%)	97.8% (96.14%, 99.52%)

The upper limit of the 95% CI for SSG final cure is 56.03%. This was considered a very conservative estimate of placebo response. The lower limit for amphotericin final cure is 96.14%. The treatment effect of amphotericin B deoxycholate, or M1, is conservatively estimated at 40.11%. Although M2 of 15% can be statistically supported, a 10% margin was thought to be clinically more acceptable because VL is a serious systemic disease.

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